ORIGINAL ARTICLE

# Risk Stratification by Ambulatory Blood Pressure Monitoring Across JNC Classes of Conventional Blood Pressure

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**BACKGROUND**
Guidelines propose classification of conventional blood pressure (CBP) into normotension (<120/<80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/≥90 mm Hg).

**METHODS**
To assess the potential differential contribution of ambulatory blood pressure (ABP) in predicting risk across CBP strata, we analyzed outcomes in 7,826 untreated people recruited from 11 populations.

**RESULTS**
During an 11.3-year period, 809 participants died (276 cardiovascular deaths) and 639, 383, and 225 experienced a cardiovascular, cardiac, or cerebrovascular event. Compared with normotension (n = 2,639), prehypertension (n = 3,076) carried higher risk ($P \le 0.015$) of cardiovascular (+41%) and cerebrovascular (+92%) endpoints; compared with hypertension (n = 2,111) prehypertension entailed lower risk ($P \le 0.005$) of total mortality (–14%) and cardiovascular mortality (–29%) and of cardiovascular (–34%), cardiac (–33%), or cerebrovascular (–47%) events. Multivariable-adjusted hazard ratios (HRs) for stroke associated with 24-hour and daytime diastolic ABP (+5 mm Hg) were higher ($P \le 0.045$) in normotension than in prehypertension and hypertension (1.98 vs.1.19 vs.1.28 and 1.73 vs.1.09 vs. 1.24, respectively) with similar trends ($0.03 \le P \le 0.11$) for systolic ABP (+10 mm Hg). However, HRs for fatal endpoints and cardiac events associated with ABP did not differ significantly ($P \ge 0.13$) across CBP categories. Of normotensive and prehypertensive participants, 7.5% and 29.3% had masked hypertension (daytime ABP ≥135/≥85 mm Hg). Compared with true normotension ($P \le 0.01$), HRs for stroke were 3.02 in normotension and 2.97 in prehypertension associated with masked hypertension with no difference between the latter two conditions ($P = 0.93$).

**CONCLUSION**
ABP refines risk stratification in normotension and prehypertension mainly by enabling the diagnosis of masked hypertension.

*Keywords:* ambulatory blood pressure monitoring; blood pressure; hypertension; masked hypertension; population science; prehypertension; risk stratification.

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The relationship between cardiovascular outcome and blood pressure (BP) is log linear, without a critical level above which the risk suddenly increases.[1] However, for the diagnosis and management of hypertension, clinicians need operational thresholds.[2,3] Therefore, the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7)[2] and the World Health Organization and the International Society of Hypertension (WHO–ISH)[3] proposed a classification of blood pressure based on conventional measurement into normal, prehypertensive, and hypertensive levels.

Ambulatory blood pressure (ABP) monitoring substantially refines the risk stratification in hypertensive patients[4] and in people randomly recruited from populations.[5,6] Few studies[7–10] have examined whether ABP measurement refines risk stratification to a similar extent within each of the categories of office blood pressure. However, these studies had a sample size that ranged from 591[9] to 942,[8] most included selected patients,[7–10] and all but 1[9] had as outcome variables intermediary outcomes, such as left ventricular mass,[7] pulse wave velocity,[8] and carotid intima-media thickness.[10] To our knowledge, no previous studies have addressed risk stratification by ABP monitoring in large population cohorts across all categories of the conventional blood pressure (CBP) using hard fatal and nonfatal outcomes. To resolve this research question, we analyzed 7,826 untreated participants randomly recruited from 11 populations and enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO).[11]

## METHODS

### Study population

At the time of writing this article, the IDACO database[11] included 11 randomly recruited population cohorts[12–20] and 12,148 participants with available data on conventional and ABP. Details on recruitment of the IDACO cohorts are given in Supplementary Table 1. We excluded 4,322 participants because they were aged <18 years (n = 303), their CBP was not within the database (n = 248), their nighttime blood pressure had not been recorded (n = 1,367[14]), they were taking antihypertensive drugs at baseline (n = 2,156), or their ABP recordings did not comply with recommended[21] and predefined[11] quality standards and covered fewer than 20 hours or included fewer than 10 daytime or 5 nighttime readings (n = 248). Thus, the total number of participants included in the present analysis totaled 7,826.

### Blood pressure measurement

Methods used for conventional and ABP measurement are described in detail in the Expanded Methods section. CBP was the average of 2 consecutive readings obtained either at the person's home[14,16–19] or at an examination center.[13,15,20,22] Portable monitors were programmed to obtain ABP readings at 30-minute intervals throughout the whole day[13,20] or at intervals ranging from 15 minutes[22] to 30 minutes[15] during the daytime and from 30 minutes[22] to 60 minutes[15] at night.

We categorized CBP according to the JNC7[2] and WHO–ISH[3] guidelines. Normal blood pressure was a level <120 mm Hg systolic and 80 mm Hg diastolic. Prehypertension encompassed 120–139 mm Hg systolic or 80–89 mm Hg diastolic. Patients who had a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic were classified as hypertensive. To categorize levels of ABP, we followed the guidelines of the European Societies of Cardiology and Hypertension.[23] Ambulatory hypertension was a 24-hour level of 130 mm Hg systolic or 80 mm Hg diastolic or more; for the daytime blood pressure, these thresholds were 135 mm Hg and 85 mm Hg, and for the nighttime blood pressure they were 120 mm Hg and 70 mm Hg, respectively. Sustained normotension and hypertension were a normal blood pressure or hypertension on both conventional and ambulatory measurement. Masked hypertension was ambulatory hypertension in participants with a normal CBP.

### Other measurements

We used the questionnaires originally administered in each cohort to obtain information on each participant's medical history and smoking and drinking habits. Body mass index was measured as body weight, in kilograms, divided by height, in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 7.0 mmol/L,[13–16,18,19,22] a random blood glucose concentration of at least 11.1 mmol/L,[13,14,17] a self-reported diagnosis,[14,16,17] or diabetes documented in practice or hospital records.[16]

### Ascertainment of events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous publications.[24–26] Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events encompassed death from ischemic heart disease, sudden death, nonfatal myocardial infarction, and coronary revascularization. Cardiac events comprised coronary endpoints and fatal and nonfatal heart failure. The composite cardiovascular endpoint included all aforementioned endpoints plus cardiovascular mortality. In all outcome analyses, we only considered the first event within each category.

### Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). For comparison of means and proportions, we applied the large-sample $z$ test and the $\chi^2$ statistic, respectively. In Cox regression, we adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. To adjust for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Kraków,

Novosibirsk, Padova, and Pilsen).[19] We ascertained that the proportional hazard assumption underlying the Cox regression models was fulfilled by testing the interaction between the blood pressure categories and follow-up time. For categorical analyses, we presented hazard ratios (HRs) as floating absolute risks and calculated their standard errors as described by Easton and colleagues.[27] This approach allows calculation of a 95% confidence interval (CI) for the relative risk in the reference group.[27] We compared HRs between groups by testing the significance of the appropriated interaction term. Statistical significance was an α level of <0.05 on 2-sided tests.

## RESULTS

### Baseline characteristics

The study population consisted of 5,488 Europeans (70.1%), 1,150 Asians (14.7%), and 1,188 South Americans (15.2%). The 7,826 participants included 3,706 women (47.4%). Mean (± standard deviation (SD)) age was 49.9 ± 15.6 years. At enrollment, 2,367 participants (30.2%) were smokers and 3,941 (50.4%) reported intake of alcohol. In the whole study population, CBP averaged (± SD) 126.8 ± 18.7 mm Hg systolic and 78.3 ± 11.0 mm Hg diastolic. The median number of readings averaged to estimate the 24-hour blood pressure was 52 (5th to 95th percentile interval, 35–81; range, 20–99); the 24-hour ABPs were 121.7 ± 13.3 mm Hg and 73.0 ± 8.1 mm Hg, respectively. These levels were 128.2 ± 14.4 mm Hg and 78.3 ± 8.8 mm Hg during daytime and 110.3 ± 13.8 mm Hg and 63.7 ± 8.7 mm Hg at night.

On CBP measurement, according to the JNC7[2]/WHO–ISH[3] criteria, 2,639 (33.7%), 3,076 (39.3%), and 2,111 (27.0%) participants were normotensive, prehypertensive, or hypertensive, respectively. Table 1 lists the characteristics of the study participants by these categories. Using conventional and daytime ABP measurement for cross-classification, the prevalence of masked hypertension was higher ($P < 0.0001$) among prehypertensive patients (n = 900; 29.3%) than those with normotension (n = 198; 7.5%). Supplementary Tables 1 and 2 and the Supplementary Results provide detailed information on the determinants of masked hypertension and their discriminative power in our untreated participants.

### Incidence of events

In the overall study population, the median follow-up was 11.3 years (5th to 95th percentile interval, 2.6–18.2 years). Across centers, median follow-up ranged from 2.5 years (5th to 95th percentile interval, 2.3–2.6) in Jingning, China, to 17.8 years (16.6–18.2 years) in Dublin, Ireland. During 87,624 person-years of follow-up, 809 participants died (9.2/1,000 person-years) and 639 experienced a fatal or nonfatal cardiovascular complication (7.5/1,000 person-years). Mortality included 276 cardiovascular and 503 noncardiovascular deaths, 23 deaths from unknown causes, and 7 deaths due to renal failure. Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke was 42 and 183, respectively. Cardiac events consisted of 39 fatal and 134 nonfatal cases of acute myocardial infarction, 45 deaths from ischemic heart diseases, 6 sudden deaths, 16 fatal and 96 nonfatal cases of heart failure, and 47 cases of surgical or percutaneous coronary revascularization.

### Risk associated with categories of CBP

In the first step of our analyses, we assessed, as as internal validation of our dataset, whether as-expected risks increased across increasing categories of CBP. Rates of mortality and fatality combined with nonfatal events increased ($P < 0.0001$) with higher categories of CBP (Table 2). With normotension as the reference (Table 2), prehypertensive participants had a significantly higher risk of a composite cardiovascular endpoint (+41%; $P = 0.01$) and stroke (+92%; $P = 0.02$). With hypertension as the reference (Table 2), the risks of cardiovascular death (−28%; $P = 0.01$), a composite cardiovascular endpoint (−34%; $P < 0.0001$), a cardiac (−33%; $P = 0.0007$) or coronary (−27%; $P = 0.02$) event, or stroke (−47%; $P < 0.0001$) were significantly lower in prehypertensive participants.

### Risks associated with ABP by categories of CBP

In the next step of our analyses, we assessed whether the ABP level measured on a continuous scale differentially contributed to risk stratification across increasing categories of the CBP. We expressed HRs for 5-mm Hg and 10-mm Hg increments in the ambulatory diastolic and systolic blood pressures, respectively.

*Mortality.* In multivariable-adjusted analyses, taking normotension as the reference, the HRs for total and cardiovascular mortality associated with diastolic (+5 mm Hg; Supplementary Table 3) and systolic (+10 mm Hg; Supplementary Table 4) blood pressures as measured by 24-hour daytime and nighttime monitoring did not differ significantly ($P \geq 0.13$) from those in prehypertensive and hypertensive participants. The only exception was the higher HR for total mortality in relation to daytime diastolic blood pressure (DBP) in hypertensive compared with normotensive participants (1.10 vs. 0.92; $P = 0.04$).

*Fatal combined with nonfatal endpoints.* In multivariable-adjusted analyses, taking normotension as the reference, the HRs for the composite cardiovascular endpoint and cardiac events associated with diastolic (Table 3) and systolic (Table 4) blood pressures as measured by 24-hour daytime and nighttime monitoring did not significantly differ ($P \geq 0.19$) from those in prehypertensive and hypertensive participants. However, the HRs for stroke associated with 24-hour and daytime DBPs were significantly ($0.005 \leq P \leq 0.04$) higher in normotensive participants than in prehypertensive and hypertensive participants. The estimates for 24-hour DBP were 1.98 vs.1.19 vs.1.28 and for the daytime DBP were 1.73 vs.1.09 vs.1.24, respectively (Table 3). A similar trend ($0.04 \leq P \leq 0.11$) was observed for stroke in relation to the 24-hour and daytime systolic blood pressures (SBPs; Table 4). The estimates for 24-hour SBP were 2.27 vs.1.39 vs.1.38 and for daytime SBP were 2.07 vs.1.20 vs.1.37.

**Table 1.** Baseline characteristics by category of conventional blood pressure

| Characteristic | Normotension | Prehypertension | Hypertension |
|---|---|---|---|
| **Number (%)** | | | |
| All participants in category | 2,639 (33.7) | 3,076 (39.3) | 2,111 (27.0) |
| European | 1,765 (66.9) | 2,156 (70.1)† | 1,567 (74.2)† |
| Asian | 381 (14.4) | 535 (17.4)† | 234 (11.1)‡ |
| South American | 493 (18.7) | 385 (12.5)‡ | 310 (14.7)* |
| Women | 1,676 (63.5) | 1,328 (43.2)‡ | 702 (33.3)‡ |
| Smokers | 875 (33.2) | 947 (30.1) | 545 (25.9)‡ |
| Drinking alcohol | 1,172 (45.0) | 1,572 (53.6)‡ | 1,197 (62.7)‡ |
| Diabetes mellitus | 73 (2.8) | 156 (5.1)‡ | 140 (6.6)‡ |
| Cardiovascular disorder | 96 (3.6) | 162 (5.1)‡ | 145 (6.9)* |
| Daytime hypertension | 198 (7.5) | 900 (29.2)‡ | 1,525 (72.2)‡ |
| **Mean ± standard deviation** | | | |
| Age, years | 42.2 ± 13.8 | 50.2 ± 15.3‡ | 59.0 ± 13.1‡ |
| Body mass index, kg/m$^2$ | 23.5 ± 3.4 | 25.3 ± 4.0‡ | 26.6 ± 4.2‡ |
| Conventional pressure (mm Hg) | | | |
| Systolic | 108.6 ± 7.3 | 126.4 ± 7.0‡ | 150.0 ± 14.4‡ |
| Diastolic | 69.0 ± 6.3 | 78.3 ± 6.8‡ | 89.7 ± 9.7‡ |
| Ambulatory pressure (mm Hg) | | | |
| 24-hour systolic | 112.6 ± 8.5 | 121.1 ± 9.3‡ | 133.9 ± 13.5‡ |
| 24-hour diastolic | 68.3 ± 5.6 | 72.9 ± 6.4‡ | 79.1 ± 8.7‡ |
| Daytime systolic | 118.5 ± 9.8 | 127.8 ± 10.5‡ | 141.0 ± 14.3‡ |
| Daytime diastolic | 73.4 ± 6.4 | 78.2 ± 7.3‡ | 84.6 ± 9.6‡ |
| Nighttime systolic | 102.5 ± 9.3 | 109.6 ± 10.7‡ | 121.0 ± 15.6‡ |
| Nighttime diastolic | 59.3 ± 6.5 | 63.5 ± 7.4‡ | 69.4 ± 9.6‡ |
| Blood glucose, mmol/L | 4.8 ± 0.9 | 5.1 ± 1.1‡ | 5.4 ± 1.4‡ |
| Serum cholesterol, mmol/L | 5.3 ± 1.1 | 5.6 ± 1.2‡ | 5.9 ± 1.2‡ |

Thresholds for the conventional blood pressure were <120/<80 mm Hg for normotension, 120–139/80–89 mm Hg for prehypertension, and ≥140/≥90 mm Hg for hypertension. Daytime hypertension was an ambulatory blood pressure of ≥135/≥85 mm Hg. To convert glucose and cholesterol from mmol/l to mg/dl, multiply by 18.01 and 38.61, respectively. Significance of the difference with the adjacent column as follows: * $P \le 0.05$, † $P \le 0.01$, and ‡ $P \le 0.001$.

### Risk associated with masked hypertension

In the last step of our analyses, with sustained normotension as the reference (Figure 1), we first explored the HRs for the composite cardiovascular endpoint and stroke associated with masked hypertension, as defined on the basis of the daytime ABP. Among participants with normotension, 198 (7.5%) had masked hypertension because of an elevated daytime systolic (98 (49.5%)) or diastolic 63 (31.8%)) blood pressure or both (37 (18.7%)). Among participants with prehypertension, 900 (29.3%) had masked hypertension, because of an elevated daytime systolic (391 (43.4%)) or diastolic (216 (24.0%)) blood pressure or both (293 (32.6%)). Compared with true normotension, the HRs associated with masked hypertension in normotensive participants were 2.11 (95% CI, 1.24–3.60; $P = 0.006$) for a composite cardiovascular endpoint and 3.02 (95% CI, 1.25–7.32; $P = 0.01$) for stroke. The corresponding HRs associated with masked hypertension in prehypertensive participants were 2.08 (95% CI, 1.67–2.59; $P < 0.0001$) and 2.97 (95% CI, 2.03–4.35; $P < 0.0001$), respectively. The HRs associated with masked hypertension compared with true normotension were similar among normotensive and prehypertensive participants ($P \ge 0.75$). Compared with prehypertension without masked hypertension, the HRs associated with masked hypertension in prehypertensive participants were 1.53 (95% CI, 1.23–1.91; $P = 0.0001$) for the composite cardiovascular endpoint and 1.48 (95% CI, 1.01–2.16; $P = 0.04$) for stroke (Figure 1).

As shown in the Supplementary Results, the above findings were consistent if we defined masked hypertension based on the 24-hour (Supplementary Figure 1) or nighttime (Supplementary Figure 2) blood pressures.

**Table 2.** Risk associated with prehypertension vs. normotension or hypertension

| | Number of endpoints (rate per 1,000 person-years) | | | Hazard ratios (confidence interval) associated with prehypertension | | | |
|---|---|---|---|---|---|---|---|
| **Endpoint** | **NT** | **PHT** | **HT** | **vs. NT** | ***P*** | ***vs.* HT** | ***P*** |
| **Mortality** | | | | | | | |
| Total | 126 (4.1) | 313 (9.0) | 370 (16.6) | 1.18 (0.96–1.46) | 0.12 | 0.86 (0.73–1.00) | 0.050 |
| Cardiovascular | 31 (1.0) | 97 (2.8) | 148 (6.7) | 1.37 (0.91–2.07) | 0.13 | 0.72 (0.55–0.94) | 0.012 |
| Noncardiovascular | 87 (2.8) | 207 (6.0) | 209 (9.4) | 1.17 (0.90–1.51) | 0.24 | 0.98 (0.80–1.20) | 0.84 |
| **Fatal plus nonfatal events** | | | | | | | |
| All cardiovascular | 77 (2.5) | 219 (6.5) | 343 (16.1) | 1.41 (1.08–1.84) | 0.012 | 0.66 (0.55–0.78) | <0.0001 |
| Cardiac | 50 (1.6) | 128 (3.7) | 205 (9.5) | 1.30 (0.93–1.83) | 0.12 | 0.67 (0.54–0.85) | 0.0007 |
| Coronary | 40 (1.3) | 98 (2.9) | 145 (6.6) | 1.25 (0.86–1.82) | 0.25 | 0.73 (0.56–0.95) | 0.020 |
| Stroke | 18 (0.6) | 76 (2.2) | 131 (6.0) | 1.92 (1.14–3.24) | 0.015 | 0.53 (0.40–0.72) | <0.0001 |

Abbreviations: HT, hypertension on conventional blood pressure measurement; NT, normotension on conventional blood pressure measurement; PHT, prehypertension on conventional blood pressure measurement.

NT (<120/<80 mm Hg), PHT (120–139/80–89 mm Hg), and HT (≥140/≥90 mm Hg) were defined according to the JNC7[2]/WHO-ISH[3] criteria. All rates increased from NT to PHT and from PHT to HT ($P < 0.0001$). Hazard ratios, presented with 95% confidence interval, express the risk compared with prehypertension. All Cox models were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus.

**Table 3.** Multivariable-adjusted hazard ratios for cardiovascular events associated with diastolic ambulatory pressure by category of conventional blood pressure

| | 24-hour | | Daytime | | Nighttime | |
|---|---|---|---|---|---|---|
| **Endpoint by subgroup** | **HR (CI)** | ***P*** | **HR (CI)** | ***P*** | **HR (CI)** | ***P*** |
| **All cardiovascular events** | | | | | | |
| Normotension | 1.32 (1.09–1.60)† | … | 1.26 (1.06–1.49)† | … | 1.18 (1.00–1.38)* | … |
| Prehypertension | 1.16 (1.04–1.29)† | 0.19 | 1.12 (1.02–1.23)* | 0.20 | 1.10 (1.01–1.21)* | 0.37 |
| Hypertension | 1.20 (1.12–1.27)§ | 0.37 | 1.15 (1.08–1.22)§ | 0.43 | 1.15 (1.09–1.21)§ | 0.67 |
| **Cardiac events** | | | | | | |
| Normotension | 1.10 (0.84–1.43) | … | 1.10 (0.87–1.38) | | 1.04 (0.83–1.29) | … |
| Prehypertension | 1.15 (0.99–1.32) | 0.93 | 1.14 (1.00–1.29)* | 0.87 | 1.04 (0.92–1.17) | 0.79 |
| Hypertension | 1.14 (1.05–1.24)† | 0.84 | 1.10 (1.02–1.18)* | 0.83 | 1.10 (1.03–1.18)† | 0.89 |
| **Stroke** | | | | | | |
| Normotension | 1.98 (1.44–2.74)§ | … | 1.73 (1.29–2.32)‡ | … | 1.61 (1.18–2.20)† | … |
| Prehypertension | 1.19 (0.99–1.43) | 0.005 | 1.09 (0.93–1.27) | 0.005 | 1.21 (1.04–1.40)* | 0.12 |
| Hypertension | 1.28 (1.16–1.41)§ | 0.016 | 1.24 (1.13–1.35)§ | 0.045 | 1.20 (1.10–1.31)§ | 0.13 |

Normotension (<120/<80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. The number of participants and cardiovascular events per group appear in Table 2. HRs, given with 95% CI, express the risk for a 5-mm Hg increase in diastolic blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. *P* values are for the comparison of the HRs in prehypertensive and hypertensive participants with the HRs in normotensive participants. The differences in the HRs between prehypertensive and hypertensive participants were all nonsignificant ($P \geq 0.074$).

Significance of the HRs: * $P \leq 0.05$; † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

Abbreviations: CI, confidence interval; HR, hazard ratio; ..., not applicable.

### Sensitivity analyses

The incidence of endpoints differed among IDACO cohorts according to ethnicity, sex ratio, and age distribution. However, our results, which describe the risk of stroke associated with 24-hour (Supplementary Tables 6 and 8) or daytime (Supplementary Tables 7 and 9) DBP, remained consistent when we excluded 1 cohort at a time (Supplementary Tables 6 and 7) or in analyses stratified by sex, age (<60 vs. ≥60 years), or ethnicity (Supplementary Tables 8 and 9).

**Table 4.** Multivariable-adjusted hazard ratios for cardiovascular events associated with systolic ambulatory pressure by category of conventional blood pressure

| | 24-hour | | Daytime | | Nighttime | |
|---|---|---|---|---|---|---|
| **Endpoint by subgroup** | **HR (CI)** | ***P*** | **HR (CI)** | ***P*** | **HR (CI)** | ***P*** |
| **All cardiovascular events** | | | | | | |
| Normotension | 1.51 (1.19–1.92)‡ | … | 1.44 (1.16–1.80)† | … | 1.30 (1.07–1.59)† | … |
| Prehypertension | 1.27 (1.10–1.45)† | 0.47 | 1.17 (1.03–1.32)* | 0.41 | 1.17 (1.05–1.31)† | 0.42 |
| Hypertension | 1.26 (1.18–1.35)§ | 0.44 | 1.24 (1.16–1.33)§ | 0.68 | 1.17 (1.11–1.24)§ | 0.36 |
| **Cardiac events** | | | | | | |
| Normotension | 1.19 (0.85–1.68) | … | 1.15 (0.84–1.57) | … | 1.12 (0.84–1.48) | … |
| Prehypertension | 1.16 (0.96–1.41) | 0.68 | 1.11 (0.93–1.32) | 0.49 | 1.04 (0.89–1.22) | 0.66 |
| Hypertension | 1.21 (1.10–1.32)§ | 0.66 | 1.18 (1.07–1.29)‡ | 0.41 | 1.14 (1.06–1.23)‡ | 0.99 |
| **Stroke** | | | | | | |
| Normotension | 2.27 (1.43–3.62)‡ | … | 2.07 (1.36–3.15)‡ | … | 1.66 (1.13–2.43)* | … |
| Prehypertension | 1.39 (1.12–1.73)† | 0.11 | 1.20 (0.99–1.46) | 0.035 | 1.34 (1.13–1.59)‡ | 0.44 |
| Hypertension | 1.38 (1.24–1.53)§ | 0.071 | 1.37 (1.23–1.52)§ | 0.099 | 1.22 (1.12–1.32)§ | 0.16 |

Normotension (<120/<80 mm Hg), prehypertension (120–139/80–89 mm Hg), and hypertension (≥140/≥90 mm Hg) refer to the JNC classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. The number of participants and cardiovascular events per group appear in Table 2. HRs, given with 95% CI, express the risk for a 10-mm Hg increase in systolic blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. *P* values are for the comparison of the HRs in prehypertensive and hypertensive participants with the HRs in normotensive participants. The differences in the HRs between prehypertensive and hypertensive participants were all nonsignificant ($P \geq 0.22$).

Significance of the HRs: * $P \leq 0.05$; † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

Abbreviations: CI, confidence interval; HR, hazard ratio; ..., not applicable.

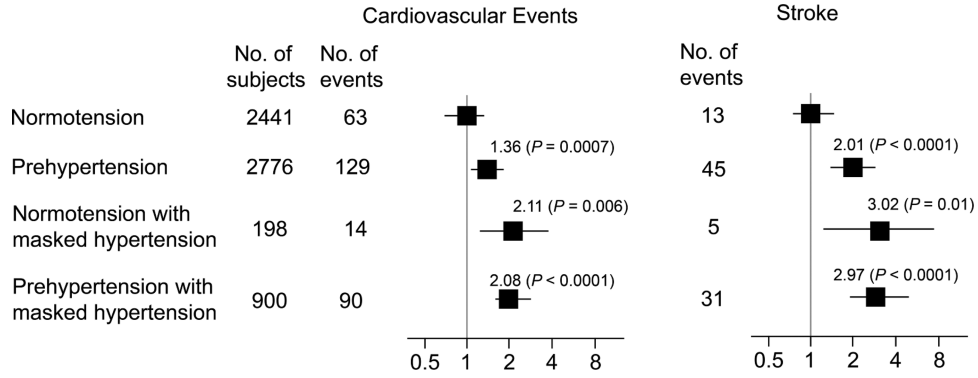


**Figure 1.** Hazard ratios for cardiovascular events and stroke associated with masked hypertension on daytime blood pressure monitoring in participants with normotension or prehypertension. Participants with sustained normotension are the reference group. Normotension (<120/<80 mm Hg) and prehypertension (120–139/80–89 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. Thresholds for daytime hypertension were ≥135 mm Hg systolic or ≥85 mm Hg diastolic. The hazard ratios (HRs) were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Horizontal lines denote the 95% confidence interval (CI). Compared with prehypertension without masked hypertension, the HRs associated with masked hypertension in prehypertensive patients were 1.53 (95% CI, 1.23–1.91; $P = 0.0001$) for the composite cardiovascular endpoint and 1.48 (95% CI, 1.01–2.16; $P = 0.04$) for stroke.

## DISCUSSION

Our current metaanalyses of patient-level data included 7,826 people not treated with blood pressure–lowering drugs. They were randomly recruited from 11 populations, and their follow-up covered, on average, 11.3 years. The key finding was that the relative risks associated with a higher ABP were similar across the 3 categories of the CBP for all endpoints under study with the exception of stroke. In normotensive and prehypertensive people with masked hypertension, the risk of cardiovascular events and stroke approximately doubled with each 10-mm Hg systolic or 5-mm Hg diastolic increase in ABP. We recently confirmed these findings in a patient-level metaanalysis of the International Database on Home blood pressure in relation to Cardiovascular Outcome using self-measured home blood pressure instead of ABP as the technique to assess the out-of-the-office blood pressure.[28] The replication of our current findings lends strong support

to the concept that out-of-the-office blood pressure measurement should be applied in normotensive or prehypertensive people with suspected masked hypertension to screen for this high-risk condition. Using the daytime ABP, in our current study, out-of-the-office blood pressure unmasked masked hypertension in 7.5% and 29.3% of participants with normotension or prehypertension on CBP, respectively. However, in the absence of any trial evidence, one can only speculate about the number of events that can be prevented by the early treatment of this condition.

Few other studies[7–10] have addressed the association between health outcomes and the ABP across categories of the CBP, as proposed by US[2] and international[3] guidelines. Most studies were only cross-sectional[7,8,10] or focused only on intermediate signs of target organ damage.[7,8,10] Zhu and colleagues studied 532 white and 410 black twins (mean age, 17.6 years). For youth aged <18 years, prehypertension was a CBP >120 mm Hg systolic or 80 mm Hg diastolic or ranging from the 90th to the 95th percentile after stratification for sex, age, and height;[29] for participants aged ≥18 years, prehypertension was a blood pressure of 120–139 mm Hg systolic or 80–89 mm Hg diastolic.[2,3] The prevalence of prehypertension was 12.0%. Cardiovascular risk factors, including obesity and high pulse wave velocity, clustered in prehypertensive participants.[8]

Manios and coworkers[10] enrolled 807 referred patients whose office blood pressure was <140 mm Hg systolic and 90 mm Hg diastolic. They applied the same criteria as we did to categorize their participants. The prevalence of pure prehypertension and prehypertension with masked hypertension was 59.9% and 19.7%, respectively. With adjustments applied, prehypertensive patients with masked hypertension had higher ($P < 0.01$) carotid intima-media thickness than prehypertensive patients without masked hypertension and normotensive patients (712 vs. 649 vs. 655 μm). Shimbo and colleagues[7] studied 813 untreated participants recruited from a worksite-based population study and obtained 9 blood pressure readings (3 at each of 3 visits over 3 weeks). Among 482 normotensive (<120/<80 mm Hg) and 287 prehypertensive (120–139/80–85 mm Hg) participants, the prevalence of masked hypertension was 3.9% and 34.1%, respectively. In multivariable-adjusted models, participants with prehypertension or masked hypertension (awake blood pressure ≥135/≥85 mm Hg) had greater left ventricular mass index than those with normotension (60.8 vs. 64.2 g/m$^2$; $P < 0.01$), but left ventricular mass index was not different among prehypertensive participants without and with masked hypertension (66.1 vs. 68.6 g/m$^2$; $P = 0.19$).

Pierdomenico and colleagues[9] completed the only study that also investigated the incidence of cardiovascular events in prehypertensive patients with (n = 120) and without (n = 471) masked hypertension. The participants were hospital staff, patients referred for reasons other than cardiovascular disease or hypertension, and volunteers. During 6.6 years of follow-up (range, 0.5–15.5 years), 29 fatal and nonfatal cardiovascular events occurred. In prehypertensive patients without and with masked hypertension, the event rates per 100 patient-years were 0.57 and 1.51, respectively. With adjustments applied for covariables, including the CBP, Cox regression showed that cardiovascular risk was significantly higher in masked hypertension than in true prehypertension (masked vs. true prehypertension, relative risk 2.65; 95% CI, 1.18–5.98; $P = 0.018$). Prehypertension and masked hypertension carry great risk to develop into hypertension. In the Flemish Study on Environment, Genes and Health Outcomes,[30] the 4-year progression rates from prehypertension to hypertension were 17.9% and 26.3% in participants aged <50 years and those aged ≥50 years, respectively. In the Copenhagen Monitoring of Trends and Determinants in Cardiovascular Disease,[31] the progression rate over 10 years was 37.3%. In multivariable-adjusted analyses, progression to prehypertension or to hypertension was associated with 10-year cardiovascular risks of 11.1% and 13.9%, respectively.[31]

We[5,32] and other investigators[33–35] demonstrated that masked hypertension carries a risk approaching that of sustained hypertension. However, the novel finding of our current study is that ABP monitoring contributes to risk stratification in people who, on the basis of their CBP, would be categorized as being at low cardiovascular risk and that masked hypertension is the driver of this risk. The present findings therefore suggest that screening for masked hypertension among prehypertensive and even normotensive people might be useful. The relationship between the cardiovascular and renal complications driven by blood pressure is continuous, at least down to a CBP level of 115 mm Hg systolic or 75 mm Hg diastolic.[1] Stroke is the complication of hypertension most closely associated with blood pressure.[36] The continuous nature of the relation with blood pressure not only holds true in hypertensive patients but in normotensive people as well.[1,37] Our current findings clearly show that the relative risk of stroke increases with the ABP in normotensive people at twice the rate observed in patients with hypertension. In addition, we demonstrated that masked hypertension in normotensive and prehypertensive patients contributes to the risk of stroke and cardiovascular complications. Our current findings suggest that ABP monitoring might be indicated in normotensive and prehypertensive people to screen for masked hypertension, a condition that confers a risk approaching that of sustained hypertension.[5] Our current data and the literature show that men, prehypertensive patients, diabetic patients,[32] smokers,[38] alcohol consumers, and individuals with increased cholesterol (≥5.7 mmol/L) are at increased risk of having masked hypertension. However, robust evidence for the routine implementation of ABP monitoring as a screening tool for masked hypertension should come from randomized clinical trials that prove that the early diagnosis of masked hypertension and treatment of this condition reduces the incidence of cardiovascular events.

The strong points of our current study are the use of ambulatory monitoring to assess blood pressure; the relatively large sample size, representing populations from Europe, Asia, and South America; and the removal of treated participants from the analysis. Nevertheless, our study also has limitations. First, the number of strokes was relatively low, so that estimates of stroke risk might be less precise than wished for. We could not differentiate between ischemic and hemorrhagic stroke. On the other hand, the probability of detecting a relation with a predictor variable increases with

the number of events. Thus, that we could already detect a statistically significant difference between normotensive and hypertensive participants in the HRs for stroke associated with the ABP might reflect a true and very strong underlying relation in normotensive people. Second, we did not determine the reproducibility of masked hypertension in the context of our current population study. However, Viera and colleagues reported prevalence rates of masked hypertension among untreated patients with a borderline elevated office blood pressure to be 54% and 53% on first and repeat assessment with an agreement of 73%.[39] Among patients who underwent repeat ambulatory monitoring for a medical indication, Ben-Dov and coworkers reported an agreement of 72%.[40] Third, most participants had their CBP measured while seated at an examination center. By contrast, in other cohorts the CBP was measured in the supine position[15] or at home.[14,17–19] Fourth, ABP monitoring was not standardized in terms of device type and intervals between successive readings, but the same SAS macro ensured that daytime was always defined in the same fashion, using short fixed clock-time intervals,[41] and that the time-weighted means were calculated identically across cohorts. Finally, binning a continuous variable such as the CBP is deemed to lose information.[42] However, we followed the categorization proposed by guidelines[2,3] for use in clinical practice and to be indiscriminately applied to adults of both sexes across the age range.

In conclusion, ABP monitoring contributes to risk stratification in normotension and prehypertension, particularly in the presence of masked hypertension. Further research should address the question whether ABP monitoring might be a cost-effective screening technique to prevent the cardiovascular complications associated with masked hypertension in patients with prehypertension[23] or even in normotensive people in whom unexplained target organ damage is present or who accumulate characteristics often associated with masked hypertension (Supplementary Results).

## SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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## DISCLOSURE

The authors declared no conflict of interest.

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# Expanded Methods and Supplementary Results

This Data Supplement has been provided by the authors to give readers additional information about their work.

Supplement to:
Brguljan Hitij J, Thijs L, Li Y, et al. Risk Stratification by Ambulatory Blood Pressure Monitoring Across JNC Classes of Conventional Blood Pressure. American Journal of Hypertension

## EXPANDED METHODS

### Study population

As described in detail elsewhere,[1] we constructed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). Studies were eligible for inclusion, if they involved a random population sample, if baseline information on the ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included both fatal and nonfatal outcomes. Details on the recruitment of participants appear in Table S1 and on the quality of the ambulatory blood pressure recordings in the Supplementary Materials associated with a recent IDACO publication.[2]

In the current study, analyzed participants were 1823 residents from Copenhagen, Denmark;[3] 851 inhabitants from Ohasama, Japan;[4] 1175 subjects from Noorderkempen, Belgium;[5] 713 older men from Uppsala, Sweden;[6] 1188 subjects from Montevideo, Uruguay;[7] 299 villagers from the Jingning County, China;[8] 204 subjects from Novosibirsk, the Russian Federation;[9] 133 from Pilsen, Czech Republic;[10] 930 from Dublin, Ireland;[11] 266 from Padua, Italy;[10] and 244 from Kraków, Poland.[10] All participants gave informed written consent. Subjects recruited in Kraków, Novosibirsk, Pilsen, and Padova took part in the European Project on Genes in Hypertension (EPOGH).[10] All participants gave informed written consent.

### Blood pressure measurement

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer,[8,10-12] with validated auscultatory[4] (USM-700F, UEDA Electronic Works, Tokyo, Japan) or oscillometric[7] (OMRON HEM-705CP, Omron Corporation, Tokyo, Japan) devices, using the appropriate cuff size, with participants in the sitting[4,5,7-12] or supine[6] position. Conventional blood pressure was the average of two consecutive readings obtained either at

the person's home[5,7-10] or at an examination center.[4,6,11,12] We programmed portable monitors to obtain ambulatory blood pressure readings at 30–minute intervals throughout the whole day,[4,11] or at intervals ranging from 15minutes[12] to 30 minutes[6] during daytime and from 30 minutes[12] to 60 minutes[6] at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala[6] or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM 630) in the other cohorts.[4-11]

The same SAS macro processed all ambulatory recordings, which generally remained unedited. The Ohasama recordings were edited sparsely according to previously published criteria.[13] Within individual subjects, we weighted the means of the ambulatory blood pressure by the interval between readings. When accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 1000 h to 2000 h in people from Europe[5,6,9-12] and South America,[7] and from 0800 h to 1800 h in Asians.[4,8] The corresponding nighttime intervals ranged from midnight to 0600 h[5-7,9-12] and from 2200 h to 0400 h.[4,8] These fixed time intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and nighttime blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels.[8,14]

We categorized conventional blood pressure according to the JNC7[15] and WHO-ISH[16] guidelines. Normal blood pressure was a level lower than 120 mm Hg systolic and 80 mm Hg diastolic. High-normal blood pressure encompassed 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Patients who had a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic were classified as hypertensive. To categorize levels of the ambulatory blood pressure, we followed the guidelines of the European Societies of Cardiology and Hypertension.[17] Ambulatory hypertension was a 24-h level of at least 130 mm Hg systolic or 80 mm Hg diastolic; for the daytime blood pressure these thresholds were

135 mm Hg and 85 mm Hg, and for the nighttime blood pressure 120 mm Hg and 70 mm Hg, respectively.

### Correlates of masked hypertension

Based on previous research,[18] we evaluated sex, age, body mass index, the level of the conventionally measured systolic and diastolic blood pressure, current smoking and drinking, serum cholesterol, history of cardiovascular complications and diabetes mellitus as potential determinants of masked hypertension. We modeled these variables using single and multivariable logistic regression. We estimated the performance of variables to differentiate between individuals with and without masked hypertension, using sensitivity, specificity, the misclassification rate and the area under the receiver operating characteristic curve. We applied Younden's index to determine the optimal discrimination limit for continuous correlates.

The difference in the HRs associated with the ABP analyzed as a continuous variable between participants belonging to different CBP categories was tested by introducing the product term between CBP category (binary variable) and ABP (continuous variable) along with the other covariables in models including the two group to be compared (normotension *vs.* prehypertension and prehypertension *vs.* hypertension).

## SUPPLEMENTARY RESULTS

### Correlates of masked hypertension

In both single (Table S1) and multiple (Table S2) logistic regression analysis, male sex, older age, higher body mass index, serum cholesterol and higher conventional systolic and diastolic blood pressure, history of diabetes mellitus and current smoking and alcohol intake correlated with masked hypertension in participants with a conventional blood pressure be-

low 140 mm Hg systolic and 90 mmHg diastolic. Younden's index the best cutoff points for the conventional blood pressure to distinguish between sustained normotension and masked hypertension were 120 mm Hg systolic and 77 mm Hg diastolic. The area under the receiver operating characteristic curve for all the above predictors combined was 0.76 for the model with dichotomized covariates and 0.77 for the model with continuous covariables, indicating moderate discrimination between true normotension and normotension associated with masked hypertension.

**Risk of masked hypertension defined on the basis of 24-h or nighttime ambulatory blood pressure.**

When we defined masked hypertension on the basis of the 24-h blood pressure (Figure S1), 112 (4.2%) and 672 (21.8%) of normotensive and prehypertensive participants had masked hypertension. Compared to true normotension, the hazard ratios associated with 24-h masked hypertension in normotensive subjects, were 2.53 (CI, 1.35–4.74; $P$=0.004) for a composite cardiovascular endpoint and 4.12 (CI, 1.54–11.1; $P$ = 0.005) for stroke. The corresponding hazard ratios associated with 24-h masked hypertension in prehypertensive subjects were in 2.18 (CI, 1.72–2.76; $P$<0.001) and 3.18 (CI, 2.13–4.75; $P$<0.0001), respectively. The hazard ratios associated with 24-h masked hypertension tended to be higher in normotensive compared with prehypertensive subjects ($P$≤ 0.12). Compared to prehypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects were 1.61 (95% confidence interval, 1.27–2.04; $P$<0.0001) for the composite cardiovascular endpoint and 1.63 (1.09–2.42; $P$ = 0.02) for stroke.

Finally, we defined based on the nighttime blood pressure (Figure S2). 202 (7.6%) and 752 (24.4%) of the normotensive and prehypertensive participants had masked hypertension. Compared to true normotension, the hazard ratios associated with nighttime masked

hypertension in normotensive subjects, were 2.17 (CI, 1.31–3.62; *P*=0.003) for a composite cardiovascular endpoint and 3.35 (CI, 1.38–8.13; *P*=0.008) for stroke. The corresponding hazard ratios associated with nighttime masked hypertension in prehypertensive subjects were 2.10 (CI, 1.66–2.65; *P*<0.0001) and 3.39 (CI, 2.36–4.89; *P*<0.0001), respectively. The hazard ratios associated with nighttime masked hypertension compared with true normotension were similar among normotensive and prehypertensive subjects (*P*≥0.41). Compared to prehypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects, were 1.46 (95% confidence interval [CI], 1.18–1.88; *P* = 0.0008) for the composite cardiovascular endpoint and 1.78 (CI, 1.24–2.56; *P* = 0.002) for stroke.

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**Table S1 | Recruitment of IDACO cohorts**

| Catchment area | Sampling frame | Starting point to recruit sample | Participation rate (%) | Nº in IDACO database |
|---|---|---|---|---|
| Nooderkempen, Belgium | Family-based random sample | Address list | 78 | 2542 |
| JingNing, Zhejiang, China | Family-based random sample | Villages, all inhabitants invited | 62 | 360 |
| Pilsen, Czech Republic | Family-based random sample | Address list | 82 | 174 |
| Copenhagen County, Denmark | Stratified random sample of women and men aged 30, 40, 50 and 60 years | Population registry | 83 | 2311 |
| Mirano (Venice), Torrebelvicino (Vicenza), Valli del Pasubio (Vicenza), Italy | Population-based sample of women and men ≥18 years | Address list | 73 | 310 |
| Ohasama, Iwate prefecture, Japan | People aged ≥40 years | Address list | 78 | 1535 |
| Niepolomice, Kràkow, Poland | Family-based random sample | Address list | 54 | 321 |
| Octyabrsky district, Novosibirsk, Russian Federation | Family-based random sample | Address list | 68 | 250 |
| Montevideo, Uruguay | Age-stratified random sample | Members of a health insurance organization | 78 | 1859 |
| Uppsala, Sweden | Men aged ≥50 year | Population census | 80 | 1143 |
| Allied Irish Bank Study | Bank employees working at branches across Ireland | All invited | 14 | 981 |

**Table S2 | Diagnostic accuracy of various predictors of masked hypertension in 5715 subjects who were normotensive or prehypertensive on conventional measurement**

| Predictor | Odds ratio | *P* | Sensitivity | Specificity | Misclassification rate |
|---|---|---|---|---|---|
| Male sex | 2.27 (1.98–2.60) | <0.0001 | 0.64 (0.61–0.67) | 0.56 (0.55–0.58) | 0.42 (0.41–0.44) |
| Age ≥41 years | 2.46 (2.10–2.88) | <0.0001 | 0.79 (0.77–0.82) | 0.39 (0.38–0.41) | 0.53 (0.52–0.54) |
| Body mass index ≥25 kg/m$^2$ | 2.01 (1.76–2.29) | <0.0001 | 0.53 (0.50–0.56) | 0.64 (0.63–0.66) | 0.38 (0.37–0.39) |
| Systolic pressure ≥120 mm Hg | 4.36 (3.76–5.06) | <0.0001 | 0.75 (0.73–0.78) | 0.59 (0.57–0.60) | 0.38 (0.37–0.39) |
| Diastolic pressure ≥77 mm Hg | 3.79 (3.29–4.35) | <0.0001 | 0.66 (0.64–0.69) | 0.66 (0.64–0.67) | 0.34 (0.33–0.35) |
| Prehypertension | 5.10 (4.33–6.01) | <0.0001 | 0.82 (0.80–0.84) | 0.53 (0.51–0.54) | 0.42 (0.40–0.43) |
| Diabetes mellitus | 1.79 (1.33–2.40) | 0.0001 | 0.06 (0.05–0.08) | 0.96 (0.96–0.97) | 0.21 (0.20–0.22) |
| Cardiovascular disease | 1.26 (0.94–1.70) | 0.13 | 0.05 (0.04–0.07) | 0.96 (0.95–0.96) | 0.22 (0.21–0.23) |
| Smoker | 1.46 (1.28– 1.68) | <0.0001 | 0.39 (0.36–0.42) | 0.70 (0.68–0.71) | 0.36 (0.35–0.37) |
| Alcohol intake | 1.95 (1.70–2.24) | <0.0001 | 0.60 (0.57–0.63) | 0.52 (0.50–0.53) | 0.43 (0.42–0.45) |
| Cholesterol ≥ 5.7 mmol/L | 1.84 (1.61–2.10) | <0.0001 | 0.50 (0.47–0.53) | 0.65 (0.64–0.66) | 0.38 (0.37–0.39) |

Normotension (<120/<80 mm Hg) and prehypertension (120-139/80-89 mm Hg) refer to the classification based on the conventional blood pressure according to JNC7[2]/WHO-ISH[3] criteria. Masked hypertension was a daytime blood pressure of ≥135 mm Hg systolic and/or ≥85 mm Hg diastolic. Values are unadjusted odds ratios. The cutoff points of the predictor variables is based on Younden's index**.** Bracketed values are 95% confidence intervals.

**Table S3 | Independent determinants of masked hypertension in 5715 subjects who were normotensive or prehypertensive on conventional measurement**

| Continuous determinants | | | Discrete determinants | | |
|---|---|---|---|---|---|
| | **Odds ratio** | ***P*** | | **Odds ratio** | ***P*** |
| Male sex | 1.41 (1.21–1.64) | <0.0001 | Male sex | 1.47 (1.26–1.72) | <0.0001 |
| Age (+10 years) | 1.09 (1.04–1.15) | <0.0001 | Age ≥41 years | 1.63 (1.37–1.94) | <0.0001 |
| Body mass index (+5 kg/m$^2$) | 1.13 (1.03–1.25) | 0.01 | BMI ≥25 kg/m$^2$ | 1.28 (1.10–1.48) | 0.001 |
| Systolic pressure (+10 mm Hg) | 1.66 (1.52–1.81) | <0.0001 | Systolic pressure ≥120 mm Hg | 2.68 (2.27–3.15) | <0.0001 |
| Diastolic pressure (+5 mm Hg) | 1.31 (1.24–1.39) | <0.0001 | Diastolic pressure ≥77 mm Hg | 2.23 (1.91–2.61) | <0.0001 |
| Diabetes mellitus | 1.52 (1.10–2.10) | 0.01 | Diabetes mellitus | 1.67 (1.22–2.29) | 0.002 |
| Smoker | 1.45 (1.25–1.69) | <0.0001 | Smoker | 1.40 (1.20–1.62) | <0.0001 |
| Alcohol intake | 1.38 (1.18–1.61) | 0.0001 | Alcohol intake | 1.37 (1.18–1.60) | <0.0001 |
| Cholesterol (+ 1 mmol/L) | 1.11 (1.04–1.19) | 0.001 | Cholesterol ≥5.7 mmol/L | 1.27 (1.09–1.47) | 0.002 |

Normotension (<120/<80 mm Hg) and prehypertension (120-139/80-89 mm Hg) refer to the classification based on the conventional blood pressure according to JNC7[15]/WHO-ISH[16] criteria. Masked hypertension was a daytime blood pressure of ≥135 mm Hg systolic and/or ≥85 mm Hg diastolic. Values are adjusted odds ratios. Odds ratios (95% confidence interval) were adjusted for all the other covariables in the model. History of cardiovascular disease was not a significant correlate of masked hypertension. The cutoff points of the discrete predictor variables were based on Younden's index**.**

**Table S4 | Multivariable-adjusted hazard ratios for death associated with diastolic ambulatory pressure by category of conventional blood pressure**

| Endpoints by subgroup | 24-h | | Daytime | | Nighttime | |
|---|---|---|---|---|---|---|
| | HR (CI) | *P* | HR (CI) | *P* | HR (CI) | *P* |
| **Total mortality** | | | | | | |
| Normotension | 0.98 (0.83–1.15) | … | 0.92 (0.80–1.07) | … | 1.01 (0.89–1.16) | … |
| Prehypertension | 1.01 (0.92–1.11) | 0.75 | 0.98 (0.91–1.06) | 0.57 | 1.05 (0.98–1.14) | 0.64 |
| Hypertension | 1.12 (1.06–1.20)‡ | 0.13 | 1.10 (1.04–1.16)† | 0.04 | 1.11 (1.06–1.17)§ | 0.19 |
| **Cardiovascular mortality** | | | | | | |
| Normotension | 1.10 (0.78–1.54) | … | 1.10 (0.82–1.49) | … | 0.97 (0.74–1.28) | … |
| Prehypertension | 1.10 (0.94–1.29) | 0.88 | 1.05 (0.91–1.21) | 0.85 | 1.09 (0.96–1.25) | 0.40 |
| Hypertension | 1.24 (1.13–1.35)§ | 0.39 | 1.21 (1.11–1.32)§ | 0.41 | 1.16 (1.07–1.26)‡ | 0.24 |

Normotension (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg) and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to JNC7[15]/WHO-ISH[16] criteria. The number of participants and deaths per group appear in Table 2. Hazard ratios (HRs), given with 95% confidence interval (CI) express the risk for a 5-mm Hg increase in diastolic blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. *P* values are for the comparison of the HRs in prehypertensive and hypertensive participants with the HRs in normotensive subjects. The differences in the HRs between prehypertensive and hypertensive participants were all nonsignificant ($P \geq 0.10$) with the exception of total mortality in relation to daytime diastolic blood pressure ($P = 0.04$). Significance of the hazard ratios: † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

**Table S5 | Multivariable-adjusted hazard ratios for death associated with systolic ambulatory pressure by category of conventional blood pressure**

| Endpoints by subgroup | 24-h | | Daytime | | Nighttime | |
|---|---|---|---|---|---|---|
| | HR (CI) | *P* | HR (CI) | *P* | HR (CI) | *P* |
| **Total mortality** | | | | | | |
| Normotension | 1.07 (0.87–1.32) | … | 0.98 (0.81–1.20) | … | 1.08 (0.92–1.28) | … |
| Prehypertension | 1.09 (0.97–1.22) | 0.79 | 1.03 (0.93–1.15) | 0.61 | 1.13 (1.03–1.24)* | 0.66 |
| Hypertension | 1.10 (1.03–1.19)† | 0.69 | 1.07 (0.99–1.15) | 0.42 | 1.10 (1.04–1.17)‡ | 0.83 |
| **Cardiovascular mortality** | | | | | | |
| Normotension | 1.32 (0.90–1.95) | … | 1.30 (0.90–1.86) | … | 1.15 (0.82–1.60) | … |
| Prehypertension | 1.24 (1.02–1.52) | 0.87 | 1.14 (0.96–1.37) | 0.99 | 1.20 (1.02–1.41)* | 0.72 |
| Hypertension | 1.32 (1.19–1.46)§ | 0.78 | 1.31 (1.18–1.45)§ | 0.63 | 1.20 (1.11–1.31)§ | 0.85 |

Normotension (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg) and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[15]/WHO-ISH[16] criteria. The number of participants and deaths per group appear in Table 2. Hazard ratios (HRs), given with 95% confidence interval (CI) express the risk for a 10-mm Hg increase in systolic blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. *P* values are for the comparison of the HRs in prehypertensive and hypertensive participants with the HRs in normotensive subjects. The differences in the HRs between prehypertensive and hypertensive participants were all nonsignificant ($P \geq 0.37$). Significance of the hazard ratios: * $P \leq 0.05$; † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

**Table S6 | Multivariable-adjusted hazard ratios for stroke associated with the diastolic 24-h blood pressure by category of conventional blood pressure with one cohort excluded**

| Subgroup | Normotension | | Prehypertension | | Hypertension | |
|---|---|---|---|---|---|---|
| | Number | HR (CI) | Number | HR (CI) | Number | HR (CI) |
| **All cohorts** | 18/2639 | 1.98 (1.44–2.74)§ | 76/3076 | 1.19 (0.99–1.43) | 131/2111 | 1.28 (1.16–1.41)§ |
| **Excluded cohort** | | | | | | |
| Ohasama | 10/2375 | 1.47 (0.87–2.48) | 43/2648 | 1.24 (0.97–1.60) | 109/1952 | 1.27 (1.14–1.41)§ |
| Jingning | 18/2522 | 1.98 (1.44–2.74)§ | 76/2969 | 1.19 (0.99–1.43) | 128/2036 | 1.28 (1.16–1.42)§ |
| Copenhagen | 11/2162 | 3.04 (1.89–4.90)§ | 57/2363 | 1.26 (1.02–1.56)* | 90/1478 | 1.27 (1.13–1.43)§ |
| Dublin | 18/2204 | 1.98 (1.44–2.74)§ | 75/2713 | 1.19 (0.99–1.43)* | 125/1979 | 1.31 (1.18–1.45)§ |
| Noorderkempen | 16/2169 | 1.95 (1.39–2.74)§ | 71/2597 | 1.20 (0.99–1.44) | 126/1885 | 1.28 (1.16–1.41)§ |
| Uppsala | 18/2601 | 1.98 (1.44–2.74)§ | 61/2836 | 1.07 (0.87–1.30) | 83/1676 | 1.24 (1.10–1.39)‡ |
| EPOGH | 18/2294 | 1.98 (1.44–2.74)§ | 75/2715 | 1.20 (0.99–1.44) | 130/1970 | 1.29 (1.17–1.42)§ |
| Montevideo | 17/2146 | 1.94 (1.38–2.74)‡ | 74/2691 | 1.22 (1.01–1.47)* | 126/1801 | 1.31 (1.19–1.45)§ |

Normotension (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg) and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to JNC7[15]/WHO-ISH[16] criteria. Number refers to the number of strokes/participants at risk. Hazard ratios (HR), given with 95% confidence interval (CI) express the risk of stroke for a 5-mm Hg increase in diastolic 24-h blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Significance of the hazard ratios: * $P \leq 0.05$; ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

**Table S7 | Multivariable-adjusted hazard ratios for stroke associated with the diastolic daytime blood pressure by category of conventional blood pressure with one cohort excluded**

| Subgroup | Normotension | | Prehypertension | | Hypertension | |
|---|---|---|---|---|---|---|
| | Number | HR (CI) | Number | HR (CI) | Number | HR (CI) |
| **All cohorts** | 18/2639 | 1.73 (1.29–2.32)‡ | 76/3076 | 1.09 (0.93–1.27) | 131/2111 | 1.24 (1.13–1.35)§ |
| **Excluded cohort** | | | | | | |
| Ohasama | 10/2375 | 1.37 (0.86–2.19) | 43/2648 | 1.05 (0.83–1.32) | 109/1952 | 1.22 (1.11–1.34)§ |
| Jingning | 18/2522 | 1.73 (1.29–2.32)‡ | 76/2969 | 1.09 (0.93–1.27) | 128/2036 | 1.23 (1.13–1.35)§ |
| Copenhagen | 11/2162 | 2.27 (1.57–3.30)§ | 57/2363 | 1.16 (0.97–1.39) | 90/1478 | 1.22 (1.09–1.35)‡ |
| Dublin | 18/2204 | 1.73 (1.29–2.32)‡ | 75/2713 | 1.08 (0.93–1.27) | 125/1979 | 1.25 (1.14–1.37)§ |
| Noorderkempen | 16/2169 | 1.73 (1.27–2.37)‡ | 71/2597 | 1.09 (0.92–1.28) | 126/1885 | 1.23 (1.12–1.35)§ |
| Uppsala | 18/2601 | 1.73 (1.29–2.32)‡ | 61/2836 | 1.01 (0.85–1.20) | 83/1676 | 1.23 (1.10–1.38)‡ |
| EPOGH | 18/2294 | 1.73 (1.29–2.32)‡ | 75/2715 | 1.09 (0.93–1.28) | 130/1970 | 1.24 (1.13–1.36)§ |
| Montevideo | 17/2146 | 1.68 (1.21–2.32)† | 74/2691 | 1.11 (0.95–1.30) | 126/1801 | 1.27 (1.15–1.39)§ |

Normotension (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg) and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[15]/WHO-ISH[16] criteria. Number refers to the number of strokes/participants at risk. Hazard ratios (HR), given with 95% confidence interval (CI) express the risk of stroke for a 5-mm Hg increase in diastolic daytime blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Significance of the hazard ratios: † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

**Table S8 | Multivariable-adjusted hazard ratios for stroke associated with the diastolic 24-h blood pressure by category of conventional blood pressure in various strata**

| Subgroup | Normotension | | Prehypertension | | Hypertension | |
|---|---|---|---|---|---|---|
| | Number | HR (CI) | Number | HR (CI) | Number | HR (CI) |
| **All cohorts** | 18/2639 | 1.98 (1.44–2.74)§ | 76/3076 | 1.19 (0.99–1.43) | 131/2111 | 1.28 (1.16–1.41)§ |
| Women | 11/1676 | 1.95 (1.23–3.10)† | 30/1328 | 1.07 (0.83–1.40) | 30/702 | 1.17 (0.96–1.43) |
| Men | 7/963 | 2.88 (1.45–5.70)† | 46/1748 | 1.29 (1.00–1.67)* | 101/1409 | 1.33 (1.18–1.49)§ |
| <60 years | 8/2301 | 2.02 (1.26–3.24)† | 17/2092 | 1.10 (0.77–1.58) | 12/910 | 1.03 (0.75–1.42) |
| ≥60 years | 10/338 | 2.14 (1.24–3.69)† | 59/984 | 1.21 (0.98–1.50) | 119/1201 | 1.33 (1.20–1.48)§ |
| Asians | 8/381 | 3.44 (1.89–6.25)§ | 33/535 | 1.15 (0.88–1.51) | 25/234 | 1.40 (1.06–1.87)* |
| Europeans | 9/1765 | 1.26 (0.64–2.45) | 41/2156 | 1.31 (1.01–1.71)* | 101/1567 | 1.31 (1.17–1.46)§ |

Normotension (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg) and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[15]/WHO-ISH[16] criteria. Number refers to the number of strokes/participants at risk. Hazard ratios (HR), given with 95% confidence interval (CI), express the risk of stroke for a 5-mm Hg increase in diastolic 24-h blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. The differences in the HRs between corresponding strata were all nonsignificant ($P \geq 0.17$). Significance of the hazard ratios: * $P \leq 0.05$; † $P \leq 0.01$, and § $P \leq 0.0001$.

**Table S9 | Multivariable-adjusted hazard ratios for stroke associated with the diastolic daytime blood pressure by category of conventional blood pressure in various strata**

| Subgroup | Normotension | | Prehypertension | | Hypertension | |
|---|---|---|---|---|---|---|
| | Number | HR (CI) | Number | HR (CI) | Number | HR (CI) |
| **All cohorts** | 18/2639 | 1.73 (1.29–2.32)‡ | 76/3076 | 1.09 (0.93–1.27) | 131/2111 | 1.24 (1.13–1.35)§ |
| Women | 11/1676 | 1.61 (1.06–2.45)* | 30/1328 | 0.97 (0.77–1.23) | 30/702 | 1.16 (0.97–1.38) |
| Men | 7/963 | 2.75 (1.42–5.33)† | 46/1748 | 1.16 (0.93–1.45) | 101/1409 | 1.26 (1.14–1.41)§ |
| <60 years | 8/2301 | 1.72 (1.12–2.64)* | 17/2092 | 1.08 (0.79–1.48) | 12/910 | 1.15 (0.87–1.53) |
| ≥60 years | 10/338 | 1.86 (1.13–3.04)* | 59/984 | 1.08 (0.90–1.30) | 119/1201 | 1.25 (1.14–1.38)§ |
| Asians | 8/381 | 2.45 (1.58–3.79)§ | 33/535 | 1.14 (0.91–1.44) | 25/234 | 1.39 (1.09–1.78)† |
| Europeans | 9/1765 | 1.13 (0.62–2.06) | 41/2156 | 1.10 (0.86–1.41) | 101/1567 | 1.25 (1.13–1.39)§ |

Normotension (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg) and hypertension (≥140/≥90 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[15]/WHO-ISH[16] criteria. Number refers to the number of strokes/participants at risk. Hazard ratios (HR), given with 95% confidence interval (CI), express the risk of stroke for a 5-mm Hg increase in diastolic daytime blood pressure and were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. The differences in the HRs between corresponding strata were all nonsignificant ($P \geq 0.09$). Significance of the hazard ratios: * $P \leq 0.05$; † $P \leq 0.01$, ‡ $P \leq 0.001$, and § $P \leq 0.0001$.

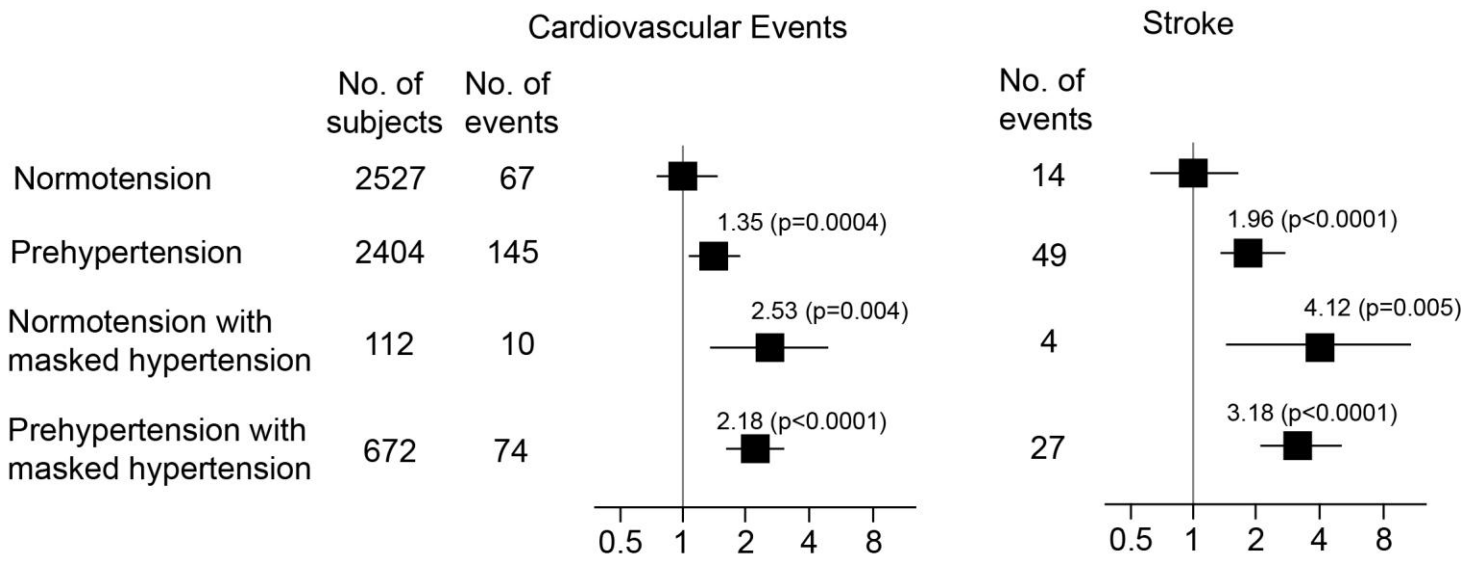



**Figure S1** | Hazard ratios for cardiovascular events and stroke associated with masked hypertension on 24-h blood pressure measurement in participants with normotension or prehypertension. Participants with sustained normotension are the reference group. Normotension (<120/<80 mm Hg) and prehypertension (120–139/80–89 mm Hg) refer to the classification based on the conventional blood pressure according to JNC7[15] and WHO-ISH[16] criteria. Thresholds for 24-h hypertension were ≥130 mm Hg systolic or ≥80 mm Hg diastolic. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Horizontal lines denote the 95% confidence interval. Compared to prehypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects were 1.61 (95% confidence interval, 1.27–2.04; *P*<0.0001) for the composite cardiovascular endpoint and 1.63 (1.09–2.42; *P* = 0.02) for stroke.

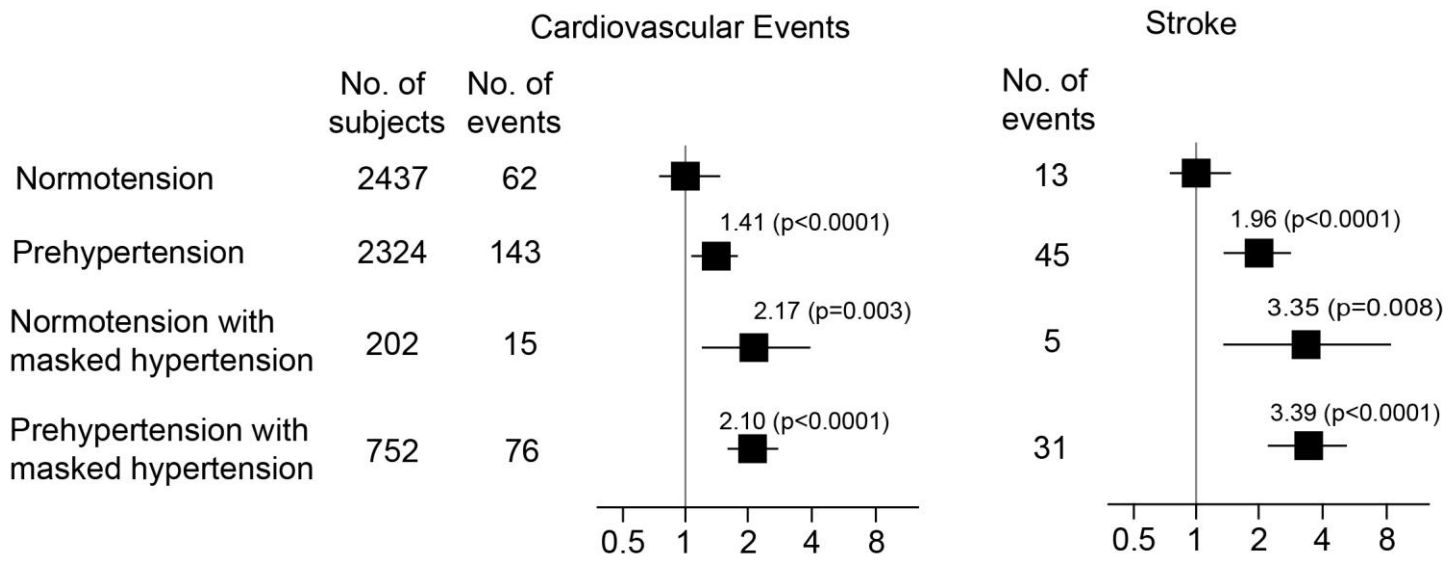
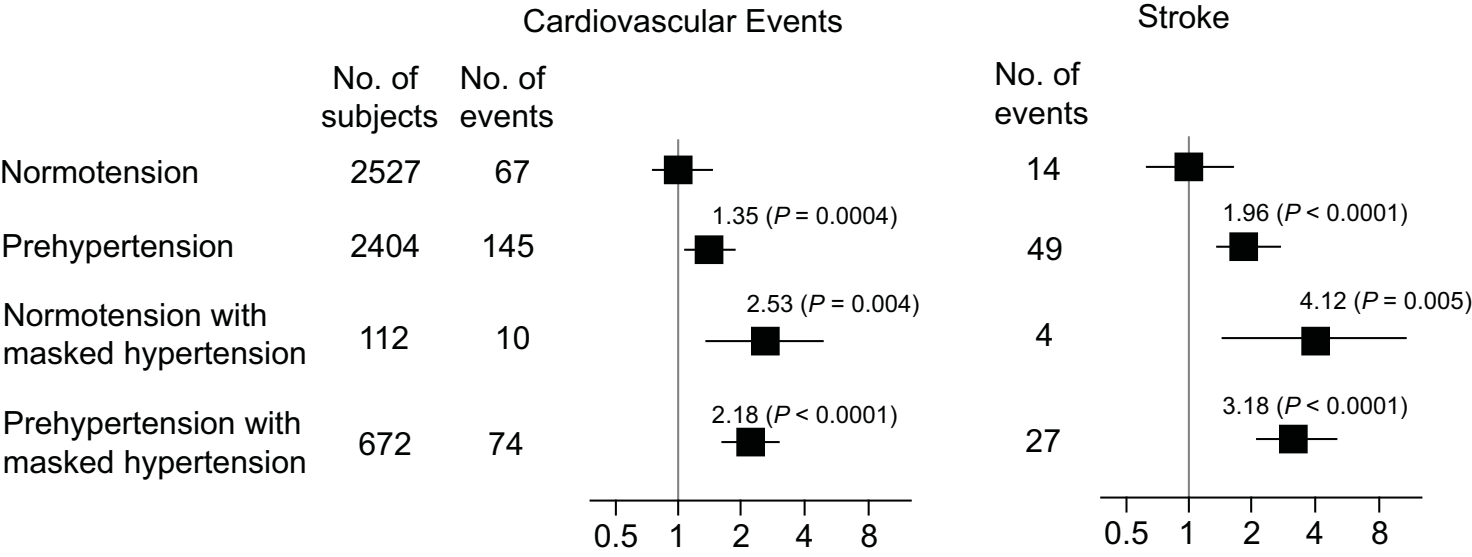
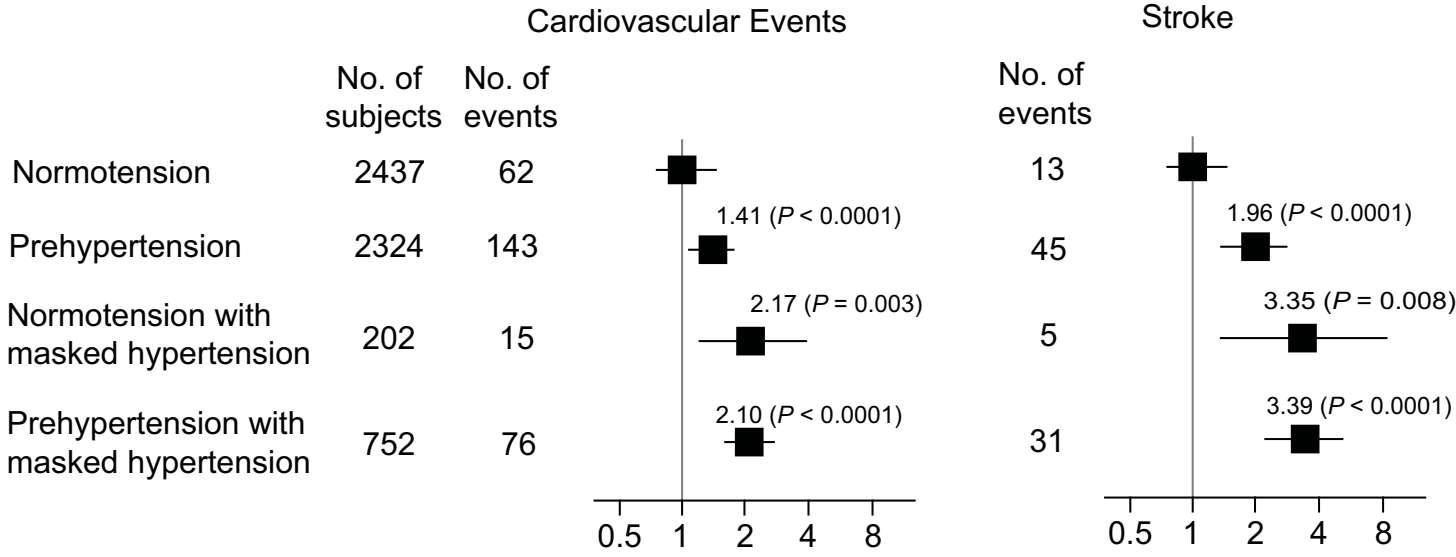



**Figure S2** | Hazard ratios for cardiovascular events and stroke associated with masked hypertension on nighttime blood pressure measurement in participants with normotension or prehypertension. Participants with sustained normotension are the reference group. Normotension (<120/<80 mm Hg) and prehypertension (120–139/80–89 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7[2]/WHO-ISH[3] criteria. Thresholds for nighttime hypertension were ≥120 mm Hg systolic or ≥70 mm Hg diastolic. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Horizontal lines denote the 95% confidence interval. Compared to prehypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects, were 1.46 (95% confidence interval [CI], 1.18–1.88; *P*=0.0008) for the composite cardiovascular endpoint and 1.78 (CI, 1.24–2.56; *P* = 0.002) for stroke.


Cardiovascular Events
Stroke
No. of subjects
No. of events
No. of events
Normotension
2527
67
14
Prehypertension
2404
145
49
1.35 (P = 0.0004)
1.96 (P < 0.0001)
Normotension with masked hypertension
112
10
4
2.53 (P = 0.004)
4.12 (P = 0.005)
Prehypertension with masked hypertension
672
74
27
2.18 (P < 0.0001)
3.18 (P < 0.0001)
0.5
1
2
4
8
0.5
1
2
4
8


Cardiovascular Events
Stroke
No. of subjects
No. of events
No. of events
Normotension
2437
62
13
Prehypertension
2324
143
45
1.41 (P < 0.0001)
1.96 (P < 0.0001)
Normotension with masked hypertension
202
15
5
2.17 (P = 0.003)
3.35 (P = 0.008)
Prehypertension with masked hypertension
752
76
31
2.10 (P < 0.0001)
3.39 (P < 0.0001)
0.5
1
2
4
8
0.5
1
2
4
8